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Mortality Risk Stratification After Traumatic Brain Injury and Hazard of Death With Titrated Hypothermia in the Eurotherm3235 Trial

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Objectives: Hypothermia reduces intracranial hypertension in patients with traumatic brain injury but was associated with harm in the Eurotherm3235 Trial. We stratified trial patients by International Mission for Prognosis and Analysis of Clinical Trials in [Traumatic Brain Injury] (IMPACT) extended model sum scores to determine where the balance of risks lay with the intervention.

Design: The Eurotherm3235 Trial was a randomized controlled trial, with standardized and blinded outcome assessment. Patients in the trial were split into risk tertiles by IMPACT extended model sum scores. A proportional hazard analysis for death between randomization and 6 months was performed by intervention and IMPACT extended model sum scores tertiles in both the intention-to-treat and the per-protocol populations of the Eurotherm3235 Trial.

Setting: Forty-seven neurologic critical care units in 18 countries.

Patients: Adult traumatic brain injury patients admitted to intensive care who had suffered a primary, closed traumatic brain injury; increased intracranial pressure; an initial head injury less than 10 days earlier; a core temperature at least 36°C; and an abnormal brain CT.

Intervention: Titrated Hypothermia in the range 32-35°C as the primary intervention to reduce raised intracranial pressure.

Measurements and Main Results: Three hundred eighty-six patients were available for analysis in the intention-to-treat and 257 in the per-protocol population. The proportional hazard analysis (intention-to-treat and per-protocol populations) showed that the treatment effect behaves similarly across all risk strata. However, there is a trend that indicates that patients in the low-risk group could be at greater risk of suffering harm due to hypothermia.

Conclusions: Hypothermia as a first line measure to reduce intracranial pressure to less than 20 mm Hg is harmful in patients with a lower severity of injury and no clear benefit exists in patients with more severe injuries. (*Crit Care Med* ; XX:00-00)

Key Words: IMPACT extended prediction model; randomized controlled trial; therapeutic hypothermia; traumatic brain injury

Experimental studies of hypothermia delivered after all forms of acute brain injury show neurologic benefit (infarct volume and neurologic behavior scores), even when the induction of hypothermia is delayed after injury and temperature reduction is modest (1). Therapeutic hypothermia (TH) has previously been tested after traumatic brain injury (TBI) to assess prophylactic neurologic protection (2).

The Eurotherm3235Trial was a large randomized controlled trial that tested TH as the primary intervention (after stage I interventions) to reduce intracranial pressure (ICP) below 20 mm Hg after TBI compared with standard care (control). In this way, TH was delivered in a dosage (depth and duration) dictated by a biomarker of the injury process, ICP, to reduce the burden of possible complications in milder injury and keeping colder temperatures for more severe injury/brain swelling. The intention-to-treat (ITT) analysis showed higher mortality and worse outcomes with TH compared with standard care, and the trial was stopped early because of likely futility and the potential for harm (3).

Postpublication sentiment has considered that TH could still be used in the TBI patients with refractory elevated ICP (4).

TBI is a heterogeneous disease with respect to cause, pathology, severity, and prognosis. This causes considerable uncertainty in the expected outcome of individual patients. Prognostic models can be used to combine different characteristics of an individual patient to predict outcome. The choice of model depends upon the clinical setting and case-mix of the population under study. The International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) models were developed on patients with moderate and severe TBI and mostly from high-income countries (5, 6). Given the data collected in Eurotherm3235Trial, the IMPACT extended model sum score (IEMSS) was selected as the most representative calculation to determine the baseline risk score for the patients, in order to assess the relationship between severity and the intervention effect.

The aim of this analysis is to assess the relationship between IEMSS and the intervention effect.

MATERIALS AND METHODS

On May 29, 2013, the Data Monitoring Committee (DMC) requested an additional analysis of the primary endpoint and mortality by IEMSS tertiles as a further participant safeguard. The first such IEMSS analysis was delivered on July 24, 2013, and after review, the DMC members decided to keep the subgroup analysis by IEMSS permanently in the DMC report. This analysis was not included in the final trial statistical analysis plan (SAP) and has not been published before but may provide important information to clinicians about the choice of therapy for ICP reduction.

Interventions and Study Procedures

The Eurotherm3235Trial was a pragmatic, randomized controlled trial, with standardized and blinded outcome assessment (7). Intracranial hypertension was defined in accordance with the Brain Trauma Foundation (BTF) guidelines, 2007 (8).

In brief, eligible participants with ICP greater than 20 mm Hg were randomized to either standard care (including mechanical ventilation and increased sedation) with

osmotherapy (control group) or standard care with titrated TH as the primary intervention to reduce ICP less than 20 mm Hg. Hypothermia was maintained for at least 48 hours and continued for as long as was necessary to maintain ICP less than or equal to 20 mm Hg, core temperature was to remain within the limits 32–35°C. Rewarming was then considered provided the ICP remained less than or equal to 20 mm Hg.

Ethical approval was obtained from Scotland A Research Ethics Committee (REC) as the lead REC (09/MRE00/34) and additionally Bradford REC (09/H1302/44) and ethics committees in a further 14 countries. Due to their incapacitated state, it was not possible to obtain consent directly from potential participants. Informed consent was therefore sought from each eligible patient's nearest relative or another person designated to give consent on the patient's behalf.

Outcomes

The primary outcome measure was the Extended Glasgow Outcome Scale (GOSE) score at 6 months after injury. The GOSE was assessed by a structured questionnaire (by post or interview), and a blinded investigator scored all outcomes according to a standardized approach (9). The 6-month mortality was a secondary outcome.

Per-Protocol (PP) Population

The PP population comprises those members of the ITT population who completed the study without a major protocol violation and who complied adequately with the administered intervention. Intervention compliance was decided using the following strategy and is described in the trial's SAP:

Step 1. If a patient was allocated to an intervention, then they should have received the allocated intervention.

Step 2. If a patient was allocated to control group, then their core temperature should be strictly equal to or greater than 36°C for at least 80% of the 48 possible temperature observations for the first 48 hours from randomization or until death (for whichever event occurred first).

Step 3. If a patient was allocated to hypothermia group, then their core temperature should be strictly greater than or equal to 32°C and strictly less than 35°C for at least 80% of the 44 possible temperature observations from 4 hours after hypothermia started until the first 48 hours from randomization or until death (for whichever event occurred first). No barbiturate infusion was permitted within the first 48 hours from randomization.

IEMSS

Sum scores were calculated for all participants using the IMPACT extended model (10) using age, motor score, pupillary reactivity, Marshall CT classification, presence of traumatic subarachnoid hemorrhage on CT, and extradural hematoma on CT (Fig. S1, Supplemental Digital Content 1, <http://links.lww.com/CCM/C471>—legend, Supplemental Digital Content 2, <http://links.lww.com/CCM/C472>). These data were routinely collected in all subjects and available in the Case Report Form. Hypoxia and hypotension values were not recorded in the Eurotherm3235Trial and were assigned “0” points (10).

The IEMSS was ordered and split into tertiles in order to generate a baseline risk profile for each patient (low, medium, and high). The population for the calculation of the risk and subsequent tertile allocation is the ITT population, so when data are filtered by compliance (i.e., PP population), the tertiles will not necessarily remain equal in terms of numbers in each. The boundaries of the (statistical) tertiles were adjusted to group patients with the same risk score (IEMSS) into the same risk category, that is, if a patient was in the low-risk category but had an IEMSS and the same risk calculation as any patient in the medium category, then they were reallocated to medium-risk tertile. Similar adjustments were made for medium-risk participants, in a way that always made the risk tertile worse instead of better.

The probabilities of 6-month outcomes were calculated as (10):

$$\text{Probability of mortality} = 1 / (1 + \exp(-2.98 + 0.256 * (\text{sum score extended model})))$$

$$\text{Probability of unfavorable} = 1 / (1 + \exp(-2.10 + 0.276 * (\text{sum score extended model})))$$

Statistical Methods

The distribution of the 6-month GOSE between the groups (hypothermia vs control) by IEMSS was compared using ordinal regression, adjusting for time from injury (< 12 vs ≥ 12 hr), including an interaction term between IEMSS and the intervention. Also a nonadjusted model was fitted. The eight-point GOSE was collapsed to six categories by pooling death with vegetative state and lower severe disability. Also, the conventional dichotomized split of the GOSE as lower moderate disability or better (favorable) versus upper severe disability or worse (unfavorable) was analyzed. For the difference in mortality, Cox proportional hazards regression (fitting intervention, IEMSS, and an interaction term) was used, and its assumptions were verified by visual inspection of the survival curves (11). Analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC). A level of statistical significance *p* value of less than 0.05 was used.

RESULTS

Data from 386 patients were available for analysis for the ITT population. Data from 257 patients were available for analysis for the PP population (Table 1). Demographic and baseline characteristics by the IEMSS tertiles are presented in Tables S1 and S2 (Supplemental Digital Content 2, <http://links.lww.com/CCM/C472>) for the ITT population. The GOSE and mortality rate distribution by intervention are presented in Figure 1. The analysis for the GOSE and mortality rate showed no significant interaction effect between the intervention and the IEMSS tertiles for the ITT and PP populations (Figs. 2 and 3).

The adjusted and nonadjusted analysis for the collapsed and dichotomized GOSE showed no statistically significant difference between the intervention for each IEMSS tertile. The odds ratio favored “control” over hypothermia in all comparisons (Fig. 2).

The proportional hazard analysis for death between randomization and 6 months by IEMSS tertile and intervention behaved similarly across high- and medium-risk strata, but there is a change in the magnitude of the effect in the lower risk cohort (Fig. 3).

The Glasgow Coma Scale (GCS) sum score at admission was less than or equal to 8 in approximately 50% of the patients in lower and medium-risk tertiles and just over 20% of patients were characterized as having a mild TBI (GCS, 13–15) on hospital admission. These were patients who suffered secondary deterioration, and a greater proportion of patients had neurosurgery (CT Marshall score V) in the medium- and high-risk tertiles but the proportions were similar, 25% and 19%, respectively (Table S2, Supplemental Digital Content 2, <http://links.lww.com/CCM/C472>).

Intracranial pathology (Table S3, Supplemental Digital Content 2, <http://links.lww.com/CCM/C472>): More extradural hematomas were evident in the low-risk tertiles compared with medium- and high-risk tertiles (as expected), with more diffuse axonal injury in the high-risk ITT cohorts and more traumatic subarachnoid hemorrhage in high (and medium) PP cohorts.

Intracranial neurosurgery (Table S4, Supplemental Digital Content 2, <http://links.lww.com/CCM/C472>): More extradural

TABLE 1. Eurotherm3235Trial Protocol Compliance

Eurotherm3235Trial Compliance	Categories	Allocated Hypothermia	Allocated Control	Overall
Intention-to-treat population (n, %)	All subjects	195 (100)	192 (100)	387 (100)
Per-protocol population (n, %)	No	70 (35.9)	60 (31.3)	130 (33.6)
	Yes	125 (64.1)	132 (68.7)	257 (66.4)
Intervention delivered (n, %)	Hypothermia	187 (95.9)	5 (2.6)	192 (49.6)
	Control	8 (4.1)	187 (97.4)	195 (50.4)
Intervention compliance (n, %)	Missing data	2	0	2
	Yes	125 (64.8)	132 (68.8)	257 (66.8)
	No	68 (35.2)	60 (31.3)	128 (33.2)

Treatment compliance to determine the per-protocol group was decided using a strategy that is described in the text and in more detail in the trial's statistical analysis plan.

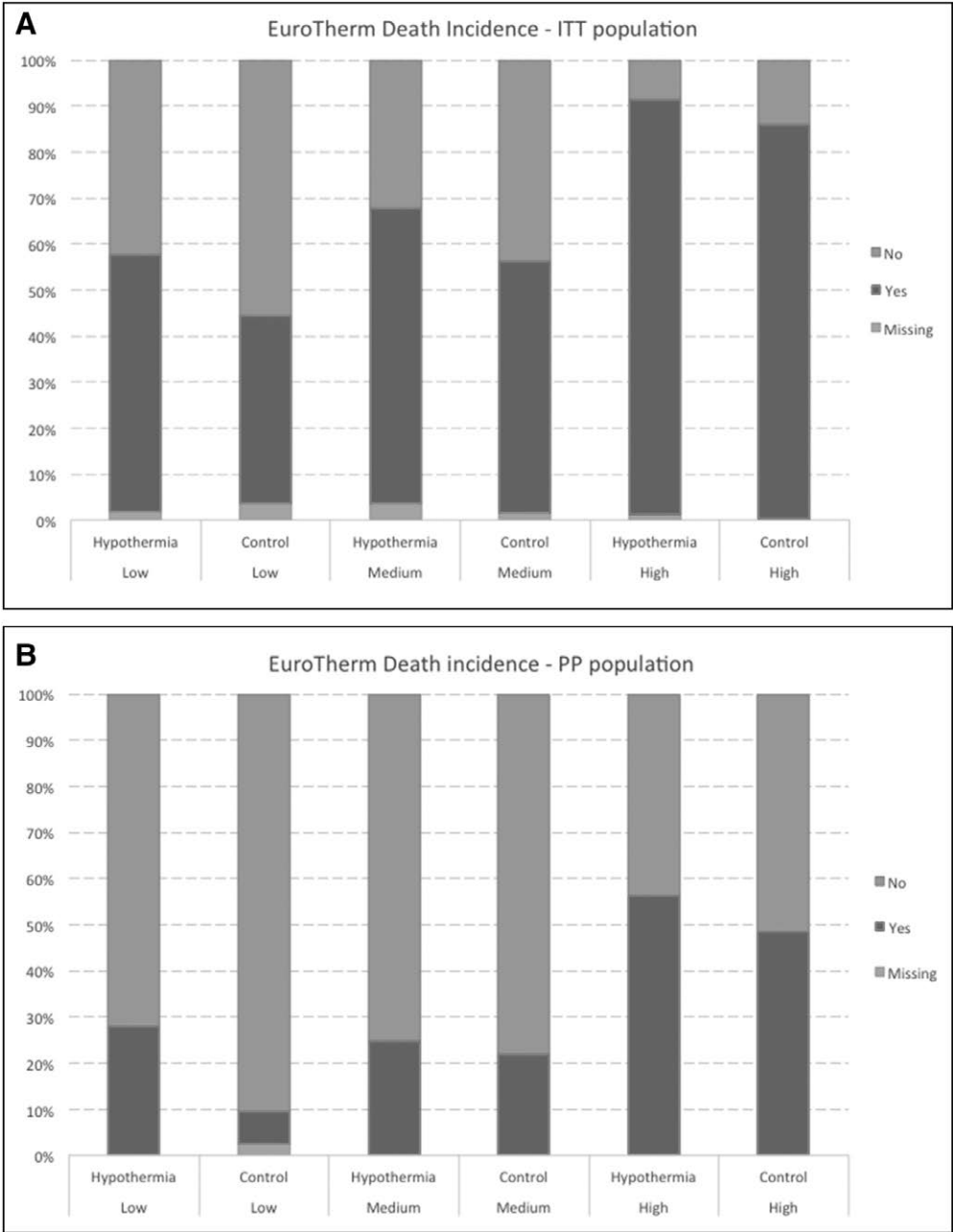


Figure 1. Bar charts showing the distribution of mortality and dichotomized Glasgow Outcome Scale Extended (GOSE) into favorable and unfavorable outcomes, by intention-to-treat (ITT) and per-protocol (PP) participant populations (four bar charts to one figure). **A.** Occurrence rate of death, ITT population. **B.** Occurrence rate of death, PP population. **C.** Glasgow Outcome Scale Extended, ITT population. **D.** Glasgow Outcome Scale Extended, PP population.

hematoma evacuations occurred in the low-risk tertiles, but the trend was otherwise for more operative interventions in the medium- and high-risk tertiles.

DISCUSSION

In summary, the analysis split by IEMSS tertiles showed a general trend toward harm for both the ITT and the PP populations with hypothermia. Furthermore, when the IEMSS was used for risk stratification of the PP population, the largest intervention effect was evident in the low-risk IEMSS group of patients who were theoretically least likely to suffer death (9% mean

probability) and unfavorable outcomes (18% mean probability) (Table 2). Consequently, it was the lowest risk of death group where the (potentially adverse) intervention effect was most evident and this intervention effect was greatest when the intervention was delivered according to the protocol (Fig. 3) (Fig. S2, Supplemental Digital Content 3, <http://links.lww.com/CCM/C473>—legend, Supplemental Digital Content 2, <http://links.lww.com/CCM/C472>). The patients with the lowest IMPACT scores are the youngest patients in the trial and when ICP is difficult to control at stage II, and because of the perception they have most to lose, they are the group in whom hypothermia is often considered as a stage III (last ditch) intervention.

Analysis of intracranial lesion(s) and neurosurgery intervention(s) did not reveal imbalances that could account for these findings. Therefore, the results of this trial could be due to either a biological effect of the hypothermia intervention or an imbalance in cointerventions, including a restriction in the use of barbiturate infusion with hypothermia.

Prediction models are important tools for heterogeneity adjustment in clinical trials and for the evaluation of the quality of care delivered to patients with TBI. The Corticosteroid Randomisation After Significant Head Injury

(CRASH) and IMPACT prognostic models have been developed using contemporary approaches to large datasets (5, 10, 12) and were externally validated reciprocally (10, 13, 14). The IMPACT model was validated against the CRASH trial data that similarly had no data on hypoxia and hypotension. We therefore followed an established methodology that demonstrated good agreement between the IMPACT EMSS and CRASH data for assessment of severity of injury.

Although randomization was extended to 10 days following review of the pilot data, the admission characteristics were used for calculation of baseline prognostic risk. The demographics

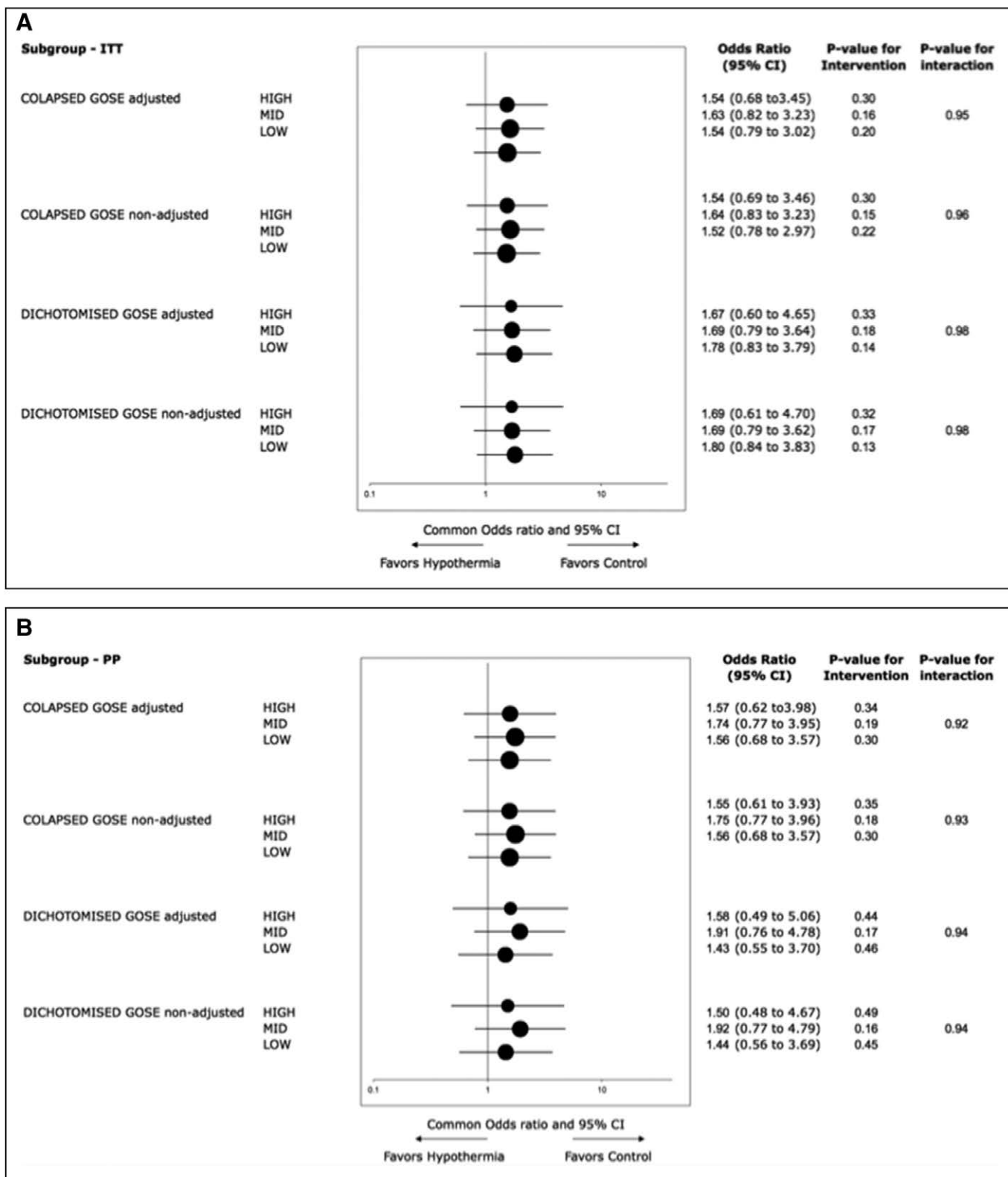


Figure 2. Forest plot of the Eurotherm3235 Trial Glasgow Outcome Scale Extended (GOSE) by intervention and International Mission for Prognosis and Analysis of Clinical Trials in [Traumatic Brain Injury] (IMPACT) Extended Model Sum Score (IEMSS). Data are analyzed by 1) collapsed ordinal analysis of the GOSE with death, vegetative state, and lower severe disability combined so as not to give credit for severely impaired survival and 2) a dichotomized analysis. Both analyses are presented with adjusted and nonadjusted (for baseline risk) outcomes. **A**, Intention-to-treat (ITT) Population. GOSE statistical analysis by intervention and IEMSS. **B**, Per-protocol (PP) population. GOSE statistical analysis by intervention and IEMSS.

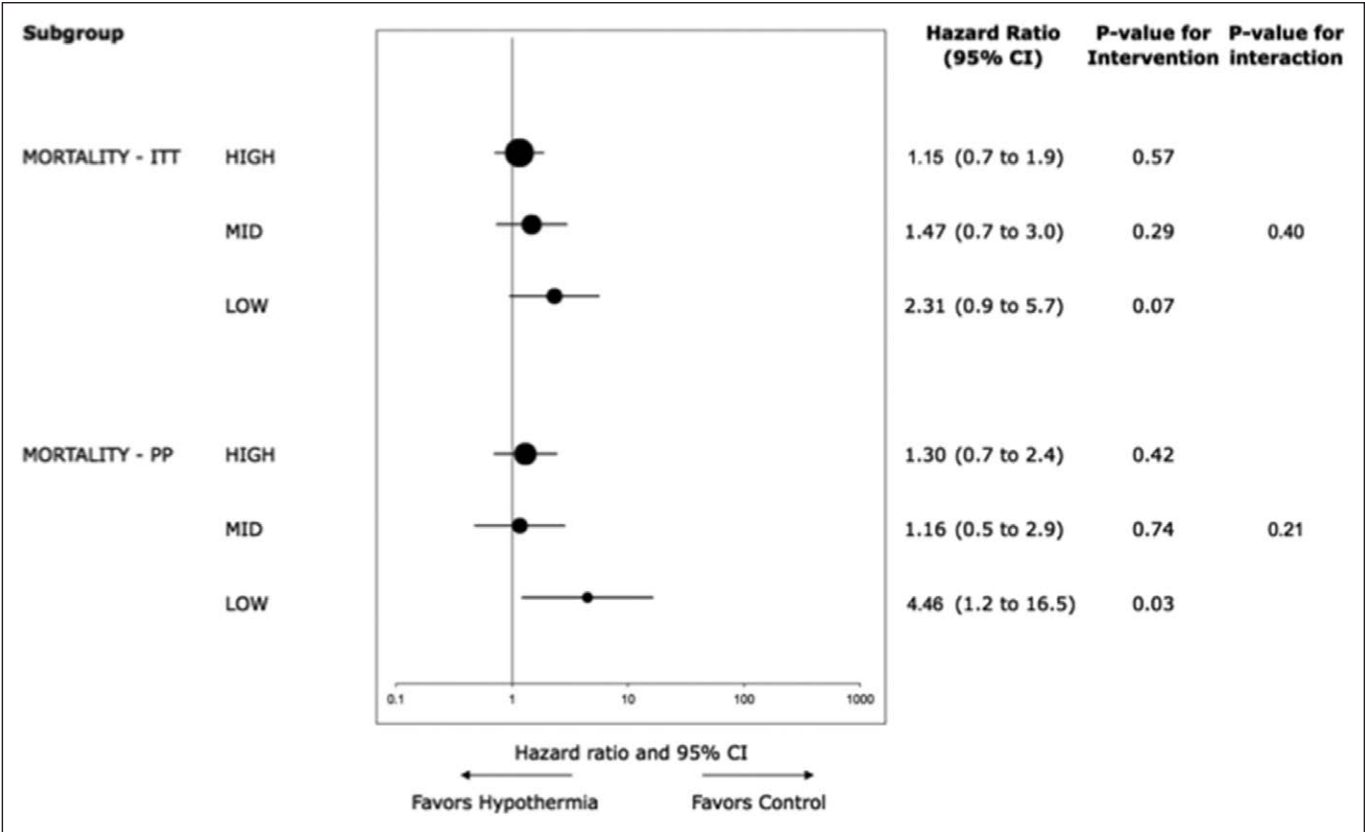


Figure 3. Forest plot of the Eurotherm3235Trial mortality by intervention and International Mission for Prognosis and Analysis of Clinical Trials in [Traumatic Brain Injury] (IMPACT) Extended Model Sum Score. Data are presented as a proportional hazard analysis for death. ITT = intention-to-treat, PP = per-protocol.

of these patients were similar to IMPACT, and the model is therefore applicable to the Eurotherm3235Trial cohort.

There were no important differences between the three tertiles for ICP control at 20 or 25 mm Hg thresholds or for new infection. When the PP patients were examined, the effect of hypothermia was to significantly increase mortality in the lowest risk tertile. The better outcome potential of the lowest risk tertile unmasked the harm of the intervention. However, no benefit was evident in the medium- and high-risk tertiles in any analyses (adjusted and nonadjusted) and the odds ratio always favored control.

The Eurotherm3235Trial protocol resulted in the use of cooling at a relatively early stage for ICP control, once the first line measures of sedation, positioning, and optimization of arterial blood gas tensions had failed. One criticism of the trial is that in many ICUs hypothermia is applied later, once other measures such as paralysis and hypertonic treatments have failed. The rationale for this trial design was to reduce the confounding effects of multiple, poorly evaluated hypertonic therapies (where the benefits and harms are not known) in the hypothermia group. The restriction of cooling to cases in which ICP control is more refractory to treatment might in effect be reserving it for those with a predicted IEMSS high risk of death. Based on these data our analysis did not demonstrate a benefit to this tertile.

At the inception of the Eurotherm3235Trial, we considered that if TH was targeted as a biomarker of the injury process, this would lead to a better balance of depth and duration of

hypothermia to injury severity. Raised ICP was considered an appropriate biomarker of TBI as it is a life-threatening complication of TBI and can result in compromised cerebral circulation, brain stem compression, and brain death. Increased ICP is strongly associated with poorer outcomes after TBI and therefore has been regarded as a target for therapy (8).

ICP monitoring is generally viewed as the cornerstone of care in these patients and is recommended in all modern guidelines for treatment of TBI. However, studies showing beneficial effects of this approach are lacking. The newly released fourth edition of the BTF guidelines (15) recommend treating ICP greater than 22 mm Hg because values above this level are associated with increased mortality. An important finding of the Eurotherm study was the efficacy of contemporary critical care management to control ICP after TBI. The Eurotherm3235Trial screening log showed ICP was controlled with first line measures in 84% of patients.

What is the benefit of ICP monitoring over and above clinical examination and cross-sectional imaging? Chesnut et al (16) and Cremer et al (17) showed no outcome benefit from ICP monitoring and an increased length of ICU and hospital stay. Previous studies that have evaluated interventions that reduce ICP are neutral or show a trend toward harm. These include Decompressive Craniectomy in Diffuse Traumatic Brain Injury) (DECRA), CRASH, Decompressive Craniectomy for Traumatic Intracranial Hypertension (RescueICP), and previous studies of TH (18–22).

TABLE 2. Predicted Mortality and Predicted Dichotomized Glasgow Outcome Score Extended Probabilities by International Mission for Prognosis and Analysis of Clinical Trials in [Traumatic Brain Injury] Extended Model Sum Score Divided into Three Tertiles

International Mission for Prognosis and Analysis of Clinical Trials in [Traumatic Brain Injury] Extended Model Sum Scores Tertile	Allocated Intervention	n	Mean	Lower 95% CI for Mean	Upper 95% CI for Mean	SD
ITT population probability of mortality ^a						
Low	Hypothermia	57	0.100	0.093	0.107	0.025
	Control	56	0.092	0.086	0.099	0.023
Mid	Hypothermia	56	0.187	0.179	0.196	0.031
	Control	64	0.192	0.184	0.199	0.031
High	Hypothermia	82	0.439	0.405	0.473	0.155
	Control	72	0.444	0.411	0.478	0.143
ITT population probability of unfavorable outcome						
Low	Hypothermia	57	0.220	0.206	0.234	0.053
	Control	56	0.204	0.192	0.217	0.048
Mid	Hypothermia	56	0.383	0.369	0.397	0.052
	Control	64	0.390	0.377	0.403	0.051
High	Hypothermia	82	0.677	0.648	0.707	0.135
	Control	72	0.686	0.657	0.715	0.124
PP population probability of mortality						
Low	Hypothermia	32	0.092	0.083	0.102	0.026
	Control	41	0.092	0.085	0.100	0.024
Mid	Hypothermia	40	0.186	0.176	0.197	0.033
	Control	41	0.190	0.180	0.199	0.030
High	Hypothermia	53	0.426	0.385	0.467	0.149
	Control	50	0.453	0.410	0.495	0.149
PP population probability of unfavorable outcome						
Low	Hypothermia	32	0.184	0.184	0.224	0.056
	Control	41	0.189	0.186	0.221	0.050
Mid	Hypothermia	40	0.363	0.363	0.398	0.055
	Control	41	0.372	0.372	0.403	0.049
High	Hypothermia	53	0.631	0.631	0.703	0.131
	Control	50	0.656	0.656	0.728	0.126

ITT = intention-to-treat, PP = per-protocol.

^aProbability calculated using the International Mission for Prognosis and Analysis of Clinical Trials in [Traumatic Brain Injury] "extended model;" Variables hypoxia and hypotension were set to "no" for all patients.

Historically, the more commonly investigated use of hypothermia following TBI has been for neuroprotection, the intervention being applied as soon as is practicable after injury. One such multicenter RCT is ongoing (Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury [POLAR-RCT]). The larger RCTs such as National Acute Brain Injury Study: Hypothermia (NABIS H) II (20), and B-HYPO (24) failed

to demonstrate a neuroprotective effect of hypothermia and many reasons have been suggested for this.

The Eurotherm3235 Trial was a study of the use of hypothermia to control ICP. We tested a widely used intervention to reduce ICP below an internationally recognized threshold and that strategy led to significantly poorer outcomes, increased mortality and, when assessed on a PP basis, harmed

participants considered at lowest risk of death, when compared with medical care that aimed to do the same. Stratification of patients according to the IEMSS (10) showed that the burden of harm was in the low risk of poor outcome and/or death cohort, with no evidence of benefit across any severity tertile.

Implications of All the Available Evidence

The four largest trials of TH after TBI all show evidence of increased mortality (3, 20, 21, 23) with TH. Therefore, despite optimistic Systematic Reviews (2), TH should not be used after TBI, for neuroprotection or to reduce ICP (4) outside of clinical trials.

CONCLUSIONS

Hypothermia as a first line measure to reduce ICP to less than 20 mm Hg is potentially harmful in patients with a lower severity of injury assessed by IEMSS and no clear benefit exists in patients with more severe injuries. We recommend against the use of hypothermia after TBI and in particular in the context of ICP reduction.

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